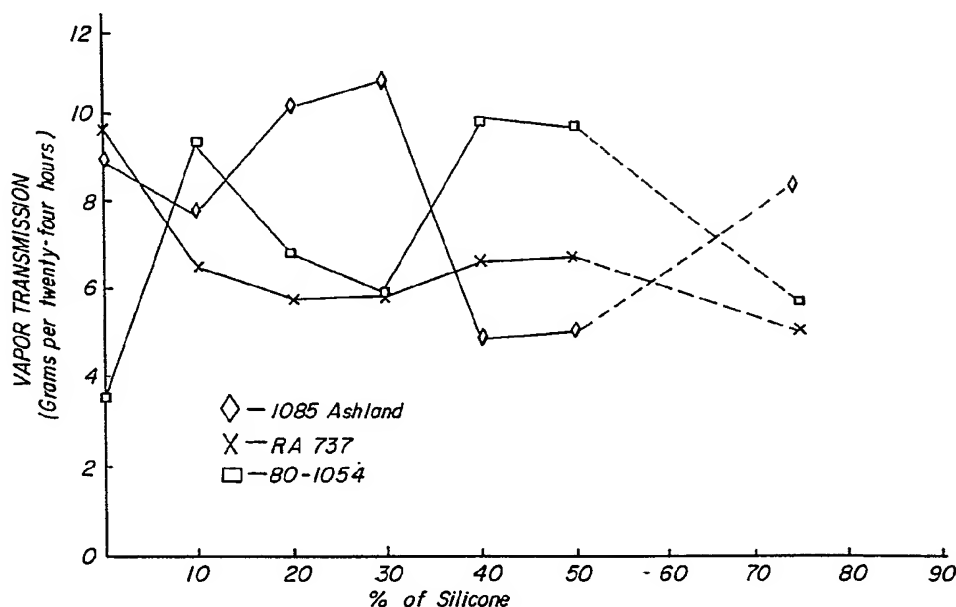




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁴ : A61K 9/00	A1	(11) International Publication Number: WO 87/ 03477 (43) International Publication Date: 18 June 1987 (18.06.87)
(21) International Application Number: PCT/US85/02425 (22) International Filing Date: 12 December 1985 (12.12.85) (71) Applicant (for all designated States except US): FLEX-CON COMPANY, INC. [US/US]; Wall Street, Spencer, MA 01582 (US). (72) Inventors; and (75) Inventors/Applicants (for US only) : PENNACE, John, R. [US/US]; 2 Knollwood Drive, Paxton, MA 01612 (US). CIUCHTA, Cheryl [US/US]; 10 Ray Street, Webster, MA 01570 (US). CONSTANTINE, David [US/US]; 23 Summit Street, Spencer, MA 01562 (US). LOFTUS, Timothy [US/US]; P.O. Box 614, Park Street, East Brook Field, MA 01515 (US). (74) Agent: KERSEY, George, E.; P.O. Box 64, Strafford, VT 05072 (US).		(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>

(54) Title: TRANSDERMAL METHODS AND ADHESIVES**(57) Abstract**

Pressure sensitive adhesives for transdermal devices. The adhesive composition is such that rates of fluid or vapor transmission can be controlled. The invention provides a fluid permeable adhesive in which a pressure sensitive polymer is blended with a cross-linked polysiloxane. Vapor or fluid transmission through the adhesive is controlled by the extent which the cross-linked polysiloxane is blended with the polymer. The adhesive can be coated on a plastic or cloth layer. The adhesive layer is protected by a release substance which is peeled upon use.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT Austria
AU Australia
BB Barbados
BE Belgium
BG Bulgaria
BJ Benin
BR Brazil
CF Central African Republic
CG Congo
CH Switzerland
CM Cameroon
DE Germany, Federal Republic of
DK Denmark
FI Finland

FR France
GA Gabon
GB United Kingdom
HU Hungary
IT Italy
JP Japan
KP Democratic People's Republic
of Korea
KR Republic of Korea
LI Liechtenstein
LK Sri Lanka
LU Luxembourg
MC Monaco
MG Madagascar

ML Mali
MR Mauritania
MW Malawi
NL Netherlands
NO Norway
RO Romania
SD Sudan
SE Sweden
SN Senegal
SU Soviet Union
TD Chad
TG Togo
US United States of America

1

TRANSDERMAL METHODS AND ADHESIVESBackground of the Invention

This invention relates to adhesives which provide suitable dermal adherence, such as to human skin. The invention relates more particularly to pressure sensitive adhesives for transdermal therapeutic devices.

Pressure sensitive adhesives for skin are typically in the form of bandages or therapeutic devices which adhere for prescribed periods of time. Such structures typically include a plastic or cloth layer that is coated with pressure sensitive adhesive. The latter is protected by a release substrate which is peeled from the adhesive when the device is to be used.

There are a number of physical characteristics that should be satisfied. The release substrate should be easily peelable from the adhesive and the latter must be sufficiently cohesive to maintain contact with skin for prescribed periods of time. In addition when the adhesive is used with human skin it must be non-toxic and not cause inflammation.

In addition transdermal therapeutic devices must meet strict performance standards. The typical transdermal device is a pouch which contains a liquid medicine that is absorbed gradually into the skin. Such devices typically contain a semi-permeable membrane and are used with absorptive drugs such as nitroglycerine or agents for cardiac treatment. Consequently any pressure sensitive adhesive that is coated on the therapeutic device must not act as a barrier to the treatment fluid.

Furthermore, since a therapeutic device remains in

1 close adhesive contact with skin over an appreciable period
of time, typically up to 24 hours, the adhesive must remain
active over the entire period. The adhesive should also per-
mit the therapeutic device to be peeled from the skin without
5 causing discomfort or leaving an objectionable residue.

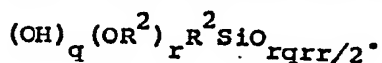
The prior art is illustrated by U.S. patents 2,857,356
and 4,039,707. In U.S. Patent 2,857,356 a pressure sensitive
adhesive is formed by the polymerization of a silicate resin
and an organopolysiloxane fluid. The silicate resin is
10 obtained by intercondensation of the cohydrolysis product of
a trialkyl hydrolyzable silane and an alkyl silicate. The
cohydrolysis product contains a number of silicone-bonded
hydroxy groups. The formulation forms a pressure sensitive
adhesive with a high degree of tack and cohesion over a wide
15 temperature range. It is principally an adhesive coating
for contacting polymeric materials such as glass and a wide
range of plastics including polyethylene. The adhesive is
also used in the manufacture of pressure sensitive tapes, but
there is no suggestion that the adhesive could be applied to
20 skin.

In order to achieve a high degree of tack and cohesive
strength, the weight ratio of silicate resin to organopoly-
siloxane fluid is between about 0.5 and 6 to 1, more prefer-
ably between about 1 to 1 and 3 to 1. Such a range would not
25 be suitable for transdermal therapeutic devices because of
insufficient tack for human skin and too great a time lapse
to achieve maximum bonding.

U.S. Patent 4,039,707 discloses a siloxane pressure
sensitive adhesive which is the intercondensation product of

-3-

1 an organopolysiloxane resin and an alkylaryl polysiloxane
gum. The organopolysiloxane resin has the formula



5 It is essential that the organopolysiloxane gum contain
aryl groups, such as phenyls, to obtain optimum pressure
sensitive adhesion. If a mixture of phenyl and methyl groups
is employed, the number of silicone-bonded phenyl groups
should be in a range such that, for each 7 to 75 phenyl
10 groups attached directly to the silicone by a carbon-silicone
linkage, there are from 29 to 25 silicone-bonded methyl
groups. A preferred range is from about 5 to 15 phenyl
groups per 95 to 85 methyl groups. Also disclosed is a
release substrate for the pressure sensitive adhesive. The
15 release substrate typically is a paper or polymer film
coated with a silanol-stopped dimethylpolysiloxane fluid.
Another disclosed release coating is a dimethylvinyl-stopped
dimethyl polysiloxane fluid.

20 Additionally, the alkylaryl polysiloxane gum should
have a viscosity from about 200,000 to 15-million centipoise
at 25°C. and contain an average from about 1.85 to 2.01 silicone-
bonded alkyl and aryl radicals per silicone atom.

25 Although the use of an alkylaryl polysiloxane gum with
an organopolysiloxane resin is disclosed in Patent 4,039,707,
there is no suggestion of combining alkylaryl polysiloxane
gums to improve adhesive, shear and liquid permeability, so
that the adhesive product could be used with transdermal
therapeutic devices.

U.S. Serial No. 451,625, filed December 20, 1982, dis-
closes a transdermal adhesive formed by the polymerization

-4-

1 product of an aryl polysiloxane, an alkyl polysiloxane and
an MQ polysiloxane with multifunctional siloxane units. This
product is suitably non-toxic and non-irritating. It also
provides suitable adhesion. It does not, however, permit
5 control over the rate of fluid passage. Consequently this
adhesive is not suitable for many medicinal applications.

Accordingly, it is an object of the invention to pro-
vide a transdermal adhesive in which the rate of fluid or
vapor transmission can be controlled. A related object is
10 to achieve a transdermal adhesive in which the rate of fluid
transmission can be specified with precision.

Another object of the invention is to provide a fluid
transmission controllable adhesive which can be used to
retain a plastic film or therapeutic device in adhesive con-
15 tact with human skin and is both non-toxic and easily remove-
able.

An important object of the invention is to provide a
fluid transmission controllable pressure sensitive adhesive
for transdermal therapeutic devices. A related object is to
20 provide a pressure sensitive adhesive which can retain a
therapeutic device in adhesive contact with skin over a pro-
longed period of time and not interfere with precision control
over the absorption of medicinal fluid.

25

1 Summary of the Invention

In accomplishing the foregoing and related objects, the invention provides a fluid permeable adhesive in which a pressure sensitive polymer is blended with a cross linked polysiloxane.

5 Vapor or fluid transmission through the adhesive is controlled by the extent to which the crosslinked polysiloxane is blended with the polymer. The vapor transmission increases and decreases in sawtooth fashion as the ratio of polysiloxane to polymer changes.

10 In accordance with one aspect of the invention, the amount of crosslinked polysiloxane ranges from more than 0 to less than 100% of the total adhesive composition. A desirable adhesive includes a crosslinked polysiloxane ranging up to 10%, up to 30% or up to 70%, depending upon the polymer.

15 In accordance with another aspect of the invention, the polymer is selected from the class of acrylics, urethanes, elastomers and blends. The final polysiloxane is formed by the crosslinking of a plurality of subordinate siloxanes which can be aryl and/or alkyl.

20 In accordance with yet another aspect of the invention, a fluid permeable adhesive is prepared by blending a crosslinked polysiloxane with an adhesive polymer which can be acrylic, urethanic, elastomeric or a blend.

25 In accordance with still another aspect of the invention, fluids can be administered to an epidermal layer through a contacting blend of a crosslinked polysiloxane and a non-silicone polymer. Fluid is then applied to the blend to permit passage through the adhesive at a prescribed rate.

-6-

1 In accordance with a further aspect of the invention, a
medical device can be provided by being partially coated with
a blend of a pressure sensitive non-silicone polymer and a cross-
linked polysiloxane.

5 A suitable catalyst for the crosslinking of polysiloxane
is a diaryl peroxide which advantageously is included to initiate
the polymerization, for example of a siloxane gum and an MQ
resin. When the catalyst is omitted the polymerization can be
initiated in other ways.

10 Although it has been widely assumed that non-silicone
polymers are incompatible with polysiloxanes, compatability can
be achieved in accordance with the invention to control vapor
transmission through the resulting adhesive blend. The end
product has characteristics that make it particularly suitable
15 for use as a pressure sensitive adhesive for transdermal thera-
peutic applications.

 In the case of a siloxane gum and resin, the weight ratio
of gum to resin is preferably in the range between 1 to 3 and
3 to 1. Where a catalyst is employed it may be between 0.1 and
20 2% by weight of the final adhesive. A preferred catalyst is
2,4 dichlorobenzoyl oxide which contains a phlegmatic agent
such as dibutylphthalate. The formulation may also include
polybutene resin in the amount up to a 15% by weight of the
final product.

25 The polymerized product is preferably prepared by forming
a raw adhesive solution of reactants and solvents such as toluene,
naphtha xylene and acetate.

-7-

1 The final adhesive can be prepared by mixing the consti-
 tuents until a homogeneous blend is formed. The blend is then
 coated on a release substrate which is typically a paper sheet
 overcoated with a silicone. This forms the desired adhesive
5 laminate. The laminate is dried to vaporize the solvents,
 after which the laminate is heated to temperatures necessary to
 initiate a polymerization reaction between the siloxane consti-
 tuents. Alternatively, the siloxane crosslinking may precede
 the blending operation.

10 The final adhesive laminate may be applied to a surface
 of a transdermal device with the adhesive coating in direct con-
 tact with the device. Preferably, the adhesive is in contact
 with a semipermeable membrane of the device. In use, the
 release is peeled away to expose the adhesive, which is applied
15 to the skin.

 The final pressure sensitive adhesive formulation exhibits
 unique liquid permeability and a high degree of adhesion to
 skin, with negligible irritation. It also has excellent
 release properties, permitting easy removal of the release
20 substrate from the adhesive.

25

Description of the Drawings

Other aspects of the invention will become apparent after considering several illustrative embodiments taken in conjunction with the drawings, in which:

5 FIGURE 1 is a graph of vapor transmission for one set of transdermal adhesives in accordance with the invention; and

 FIGURE 2 is a graph of vapor transmission for another set of transdermal adhesives in accordance with the invention.

1

Detailed Description

The pressure sensitive adhesive of the invention is a blend of a polymer and a cross-linked polysiloxane. The polysiloxane may be formed from siloxane gums, or one or more siloxane gums and one or more siloxane resins.

Suitable siloxane gums are dimethyl siloxane and dimethyldiphenyl siloxane. The term "gum" denotes a relatively high viscosity material, e.g. greater than about 20,000 centipoise. Such gums include linear alkyl/aryl polysiloxanes or polydiorganosiloxanes that can be converted from a highly viscous plastic state into a predominantly elastic state by cross-linking. W. Noll, "Chemistry and Technology of Silicones", Academic Press, New York (1958), page 387. Siloxane gums are also known as "organosiloxane elastomers".

15

The term "resin" refers to a siloxane polymer.

The pressure sensitive adhesive resulting from the blend of a cross-linked polysiloxane and a polymer is useful for attaching transdermal therapeutic devices to human skin for periods up to about 24-hours. The adhesive exhibits a favorable peel release and a high degree of adhesion over a long period. The adhesive is particularly suited to medical applications by being easily removable and non-irritating. The adhesive permits the medication in the transdermal device to pass through the adhesive into the skin.

25

Transdermal devices known in the art are formed by a semipermeable, microporous membrane, or membranes, for storing liquid medication and releasing the medication at a prescribed rate over a prolonged period. The transdermal device containing liquid medication is applied directly to the skin as a bandage.

-10-

1 The semipermeable membrane in contact with the skin is provided
with an adhering pressure sensitive layer.

U.S. patents 4,200,093 and 4,201,211 disclose representa-
tive transdermal devices with which the adhesive of the invention
5 can be used.

In general the adhesive of the invention is applicable to
all transdermal devices which must be placed in adhesive contact
with skin.

Adhesives for transdermal therapeutic devices should satisfy
10 a number of requirements. The adhesive should allow uninterrupted
liquid flow over a prolonged period, up to six hours and preferably
24 to 36 hours and longer. The flow is desirably at a constant
rate through the semipermeable membrane into the skin. Therefore,
the adhesive cannot form a barrier between the membrane and the
15 skin during use, and should not measurably retard the flow of
medicine. The adhesive of the invention satisfies the foregoing
requirements and is to be contrasted with conventional pressure
sensitive adhesives which significantly retard the throughflow
of liquids, particularly over prolonged periods.

20 Additionally the adhesive should not cause undue skin
irritation, including swelling, redness or itching on prolonged
contact. The adhesive should also allow relatively easy removal
without discomfort. Nor should the adhesive deteriorate or peel
or loosen over the period of application. Moreover, there should
25 be little or no adhesive residue remaining on the skin after the
transdermal device is removed.

A pressure sensitive adhesive blend in accordance with the
invention, which satisfies the above requirements, is presented

-11-

1 as Formulation A of Table I. Formulation A is composed of raw adhesive solutions which are dried to evaporate the solvents and then cured to form the polymerized adhesive product of Table I.

5 The acrylic resin of Table I is a self cross-linking product sold under the designation "80-1054" (JDM-808)" from National Adhesives. It is mixed with a suitable solvent such as toluene, naphtha, xylene or n-butyl acetate. No catalyst is needed since this resin is self cross-linking.

10 The cross-linkable polysiloxane is formed from a mixture of MQ resins. An MQ resin is formed from monofunctional and quadrifunctional siloxane units and has the generic chemical formula (1):



where $M = R_3SiO_{1/2}$,

15 $Q = SiO_{4/2}$, and

$R =$ preferably a methyl group.

R may also include other alkyl groups, particularly C_1 to C_4 , i.e. methyl to butyl. In particular the siloxane gum plus MQ resin of Table I e.g. SR6574 is a mixture of dimethyl-diphenyl siloxane gum and an MQ resin that is separately available under the trade name CR542 from the General Electric Company. In general the combination of an MQ resin or other organopolysiloxane resin is mixed with a methyl/phenyl siloxane gum which typically has a viscosity between 20,000 and 10,000,000 centipoise at 25°C., preferably between 20,000 and 1,000,000 centipoise. The molar ratio of phenyl groups to methyl groups in dimethyl/diphenyl siloxane gum is at least about 0.1 to 1 and preferably in the range up to 0.2 to 1. Another suitable MQ resin is sold under the name C42 -2109 of the Dow Corning Company of Midland, Michigan.

-12-

This resin mixed with dimethyl siloxane gum is available under the designation 280A from the Dow Corning Company.

The preferred catalyst is a diaryl peroxide type such as that containing 2,4 dichloro benzoyl peroxide, which contains a phlegmatic agent such as dibutyl phthalate. Such a catalyst is available under the tradename CADOX TDP from the Noury Chemical Company of Burt, New York.

Suitable solvents of Table I are toluene, naptha, xylene and butyl acetate. Other solvents may be used including ester ethyl acetate.

Although the catalyst of Table I is preferably a dichloro peroxide, other catalysts may be employed, such as diacyl peroxide, amino-salines, secondary or tertiary amines; or an organic tetanate, such as terrabutyl titanates available under the tradename TYZOR TBT from the DuPont Company of Wilmington, Delaware. Alternatively, the catalyst may be omitted and polymerization initiated in other ways, such as by radiation or electron beams.

The raw adhesive constituents such as those in Table I are mixed in a suitable vat until a homogenous solution is achieved. Although the components may be added in any order, it is advantageous to pre-mix the catalysts and solvents followed by the addition of the remaining constituents.

The homogenous raw solution is then coated on a release substrate typically a paper sheet with a release coating, such as a conventional silicone release fluid. An appropriate silicone release fluid is polydimethylvinyl silicone with appropriate catalysts, including a noble metal complex. The overcoated release substrate forms an adhesive laminate which is dried, typically in conventional convective driers operating between about 100°F and 200°F. The solvents are evaporated from the raw adhesive.

- 13 -

The dried adhesive laminate is then cured in an oven at a temperature between 200°F and 350°F, where crosslinking occurs.

The adhesive laminate containing the cured product may be transferred directly to a surface of transdermal therapeutic device, such as the semipermeable membrane. The transfer may be accomplished by passing the laminate and semipermeable membrane of the therapeutic device through a conventional laminate. The adhesively coated membrane is then shaped to match the associated transdermal. In the use of the device, the patient peels the release substrate from the laminate to expose the adhesive membrane so that direct contact can be made between the adhesive and skin.

As noted in Table I, the resulting product has a vapor transmission of 9.42 grams per 24 hour period. This result is indicated in the graph of Fig. 1 for a 10% silicone blend with 90% acrylic resin. Other vapor transmission results for other blends and other constituents are also summarized in Fig. 2. It is to be noted that for both Figs. 1 and 2 that the invention permits control over vapor transmission by controlling the ratio of the constituents in the blend.

The vapor transmission data of the Examples and Figures 1 and 2 were obtained by testing adhesive, with a thickness of 1.5 mils, placed in a standard testing cup on a urethane film with a thickness of one mil. As a result the data include the influence of the film, which has an average weight loss of 14 grams per 24 hours for a cup with a surface area of about 7 square inches.

The testing is conducted in accordance with ASTM (American Society for Testing and Materials) E96-80, for which "E96" is the fixed designation and "80" is either the year of adoption or the year of last revision.

- 13 A -

In accordance with Standard Test Method E96-80, the Water Method is used with a cup that contains distilled water. Water Vapor transmission rate is the steady water vapor flow in unit time through unit area of a body, normal to specific parallel surfaces under specified conditions of temperature and humidity.

The test cup is of noncorroding material, impermeable to water or water vapor. The mouth of the cup is at least 4.65 in.² (3000 mm²). An external flange or ledge around the mouth is used to attach the specimen. Since the specimen is an adhesive it is supported by a membrane which is masked so that the mouth area defines the test area.

The cabinet where the test cup is placed has a controlled temperature and relative humidity. The temperature is between 70 and 90°F (21 and 32°C), and maintained constant within 1°F (0.6°C). A temperature of 90°F (32°C) is recommended. The relative humidity is maintained at 50 ± 2%. Air is continuously circulated throughout the chamber, with a sufficient velocity to maintain uniform conditions.

Distilled water is used in the test cup. The sealant used for attaching the specimen is resistant to the passage of water vapor. Molten asphalt or wax is used. The sample is of uniform thickness.

The specimen is attached to the cup by sealing so that the cup mouth defines the area of the specimen exposed to the vapor pressure in the dish.

The test cup is filled with distilled water to a level $3/4 \pm 1/4$ in. (19 ± 6 mm) from the specimen. The resulting air space has a small vapor resistance.

If the equivalent water vapor transmission (WVT) is desired, it can be obtained from equation (1).

- 13 B -

$$WVT = G/tA \quad (1)$$

where G = weight change

t = time in hours

A = test area (effective mouth area)

When metric units are employed WVT is in grams per square meter per hour. When inch-pound units are employed the result is in grains per square foot per hour.

The characteristics of the support member can be compensated in standard fashion when it is desired to know the water vapor transmission characteristics of the adhesive alone.

Determination of the water vapor transmission can be determined from equation (2).

$$\frac{1}{V_t} = \frac{1}{V_m} + \frac{1}{V_a} \quad (2)$$

where V_t = total vapor transmission for membrane and adhesive sample

V_m = vapor transmission of the membrane alone

V_a = transmission of the sample

For example, if the total vapor transmission is 9.0 gms for a sample of 1.5 mils in thickness on a membrane of 1.0 mils with a vapor transmission of 14.0 gms, equation (2) becomes equation (3):

- 13 C -

$$\frac{1}{9} = \frac{1}{14} + \frac{1}{V} \quad (3)$$

The result is $V_a = 25.2$ grams for the vapor transmission of the sample. Since the sample has a thickness of 1.5 mils, the transmission per mil is given by equation (4).

$$V_a/\text{mil} = V_a \times t_a \quad (4)$$

where t_a = thickness in mils

$$V_a/m = 25.5 \times 1.5 = 37.8\text{gms} \quad (5)$$

Equation (5) is for a surface area of about 7.0 square inches (and 24 hours). To convert to equation (1) equation (5) is divided by 24 (the number of hours) and multiplied by 221.43 (the reciprocal of the area in square meters).

- 14 -

1

TABLE IPressure Sensitive Adhesive (PSA) - Formulation A

Raw Adhesive

Acrylic resin

5	(e.g. 80-1054)	39.6 grams
---	----------------	------------

Siloxane gum plus MQ resin

	(e.g. SR6574)	4.41 grams
--	---------------	------------

Catalyst

	(e.g. CADOX TDP)	0.44 grams
--	------------------	------------

10	Solvent 1	42.16 grams
----	-----------	-------------

	Solvent 2	11.35 grams
--	-----------	-------------

	Temperature	24°C.
--	-------------	-------

	Relative Humidity	38%
--	-------------------	-----

Polymerized Pressure Sensitive Adhesive Product A

15	Acrylic resin	90%*
----	---------------	------

	Siloxane gum plus MQ resin	10%*
--	----------------------------	------

	Catalyst	1%*
--	----------	-----

	Coating weight	1.5 mils
--	----------------	----------

	Vapor Transmission	9.42 grams per 24 hours
--	--------------------	-------------------------

20	*Percentage of final adhesive composition	
----	---	--

Example VI

Example V was repeated except that the acrylic resin was reduced to 50% of the final composition and siloxane increased to 50%. 54.55 grams of wet adhesives were used with 53.00 grams of wet siloxane. The peroxide was 0.532 grams. The vapor transmission as noted in Fig. 1 was 9.83 grams.

Example VII

Example VI was repeated except that the acrylic resin was reduced to 25% and the siloxane correspondingly increased to 75%. 29.3 grams of wet acrylic were used; 56.77 grams of wet siloxane, and peroxide was 0.569 grams. As noted in Fig. 1, the vapor transmission after 24 hours was 5.78 grams.

Example VIII

Example VII was repeated except acrylic resin was increased to 90% and siloxane was a gum sold under the designated C-154 of the SHS Silicone Corp.'s (lot P3404). The percent solids of the siloxane gum was 54.14%, 80.8 grams of wet acrylic, 8.24 grams of wet gum. The catalyst was 0.437 grams of peroxide. The vapor transmission after 24 hours amounted to 7.77 grams.

Examples IX through XIV

Prior examples were repeated with a pressure sensitive acrylic solution resin designated as "1085" from Ashland with 45.1% solids which were used in place of the acrylic in the prior examples. In all cases 1% peroxide was used. For 100% of acrylic and no siloxane, vapor transmission was 9.06 grams. For 90% acrylic, 10% siloxane, vapor transmission 7.69 grams; for 80% acrylic, 20% siloxane, vapor transmission 10.24 grams; for 70% acrylic, 30% siloxane, vapor transmission 10.82 grams; for 60% acrylic, 30% siloxane, vapor transmission 4.92 grams; for 50% acrylic, 50% siloxane, vapor transmission 5.04 grams. Using a pure film as a control with no adhesive, the vapor transmission in the first experiment was 14.1 grams and 13.9 grams in the second experiment.

-16-

Examples XV through XVII

The prior examples were repeated with an electronbeam curable adhesive from PPG Industries, designated SR9133A which was substituted for the acrylic in the prior examples.

For 100% adhesive and no siloxane the vapor loss was 7.5 grams, corresponding to vapor transmission 2380.88 grams per sq. meter per 24 hours.

For 80% adhesive and 20% siloxane, vapor loss of 8.04 grams, corresponding to transmission 2552.30 grams per sq. meter per 24 hours.

For a 50% mix of adhesive and siloxane, vapor loss 1.3 grams, corresponding to a transmission 2580.87 per sq. meter per 24 hours.

Examples XVIII through XXI

The foregoing were repeated with rubber-base adhesive substituted for acrylic. The rubber base adhesive had the designation V-88 and 72-9494 (8320) from National Starch.

With 70 rubber-base adhesive and 30% siloxane, the vapor loss was 2.56 grams, corresponding to 812.67 grams per sq. meter per 24 hours.

For 60% rubber-base adhesive and 40% siloxane, vapor loss was 4.36 grams (1379.7 grams per sq. meters per 24 hours).

For a 50/50 blend, the vapor loss was 4.36 grams while for 25% rubber-base adhesive and 75% siloxane, the vapor loss was 9.16 grams or 2898.7 grams per sq. meter per 24 hours.

Examples XXII through XXV

The foregoing examples were repeated with a siloxane rubber compound C-154 substituted for prior siloxanes. The results for a 10%-90% blend are reported in Example VIII.

For 20% siloxane rubber and 80% acrylic, the loss was 8.61 grams (27204.6).

For 30% rubber siloxane and 70% acrylic, loss was 6.6 (2088.6).

For 40% rubber siloxane and 60% acrylic, loss was 7.78 (2462.0).

Examples XXVI through XXVIII

The prior examples were repeated with fluorosil gum substituted for the prior siloxanes. This gum was available under the LS420 in ethyl acetate solvent. For 20% gum and 80% acrylic vapor loss 45.19 (1647.56).

For 30% gum and 70% acrylic, vapor loss was 6.06 (1923.75).

For a 50/50 blend, loss was 4.51 (1431.7).

For the film alone without any gum, the loss varied between 12.58 grams (3993.52) and 15.51 grams (4954.47).

When the 6574 siloxane was superimposed on the film with the thickness of 1.5 mils., the loss significantly decreased to 6.02 grams (1911.05).

Examples XXIX through XXXV

The foregoing procedures were repeated with an acrylic pressure-sensitive adhesive from Monsanto, RA737 (V-75) (lot 7081) substituted for the prior acrylic.

For 100% acrylic the vapor loss was 9.66.

For 90% acrylic and 10% siloxane, the loss was 6.5.

For 80% acrylic and 20% siloxane, the loss was 5.82.

For successive reductions to 70 - 65 - 50 and 25% acrylic, corresponding losses were: 5.84 - 6.66 - 6.82 and 5.12.

Examples XXXVI and XXXVII

When urethane was substituted for the acrylic, 100% urethane gave a vapor loss of 3.2 grams while 90% urethane and 10% siloxane gave a loss of 3.36 grams

WHAT IS CLAIMED IS:

1. A fluid permeable adhesive, comprising
a pressure sensitive polymer and
a cross-linked polysiloxane blended with said polymer.
2. The adhesive of claim 1 wherein said polymer is
selected from the class consisting of acrylics, urethanes,
elastomers and blends thereof.
3. The adhesive of claim 1 wherein said cross-linked
polysiloxane is formed by the cross-linking of a plurality of
subordinate siloxanes.
4. The adhesive of claim 3 wherein said subordinate
siloxanes are aryl and/or alkyl.
5. The adhesive of claim 3 wherein said polysiloxane
is formed by cross-linking with a resin.
6. The adhesive of claim 5 wherein said resin is MQ
organopolysiloxane or a fluororesin.
7. The adhesive of claim 1 wherein said polysiloxane
is cross-linked by a catalyst further including a peroxide.
8. The adhesive of claim 7 wherein said peroxide is
2,4 dichlorobenzoyl peroxide.
9. The adhesive of claim 1 wherein said cross-linked
polysiloxane ranges from more than zero to less than 100 per-
cent of the total adhesive composition.
10. The adhesive of claim 9 wherein said cross-linked
polysiloxane ranges up to 10 percent.

- 19 -

11. The method of preparing a fluid permeable adhesive which comprises the steps of

- (a) providing a cross-linked polysiloxane; and
- (b) blending said cross-linked polysiloxane with a non-silicone adhesive polymer.

12. The method of claim 11 wherein said adhesive polymer is an acrylic, a urethane, an elastomer, or a blend of the foregoing.

13. The method of administering fluids through the skin which comprises the steps of

- (a) applying a blend of a cross-linked polysiloxane adhesive and a non-silicone pressure sensitive polymer in contact with an epidermal layer; and
- (b) applying fluid to said blend to permit passage there-through at a prescribed rate.

14. A fluid permeable adhesive as defined in claim 1 further comprising a medical device at least partially coated by said adhesive.

15. A fluid permeable adhesive as defined in claim 14 further including an epidermal layer adhered to said medical device by said adhesive.

16. A method as defined in claim 10 wherein the ratio of said cross-linked polysiloxane to said adhesive polymer determines the vapor transmission therethrough.

17. The method as defined in claim 16 wherein the vapor transmission through said adhesive increases as said polysiloxane is added until it reaches a first maximum and thereafter decreases for further polysiloxane additions.

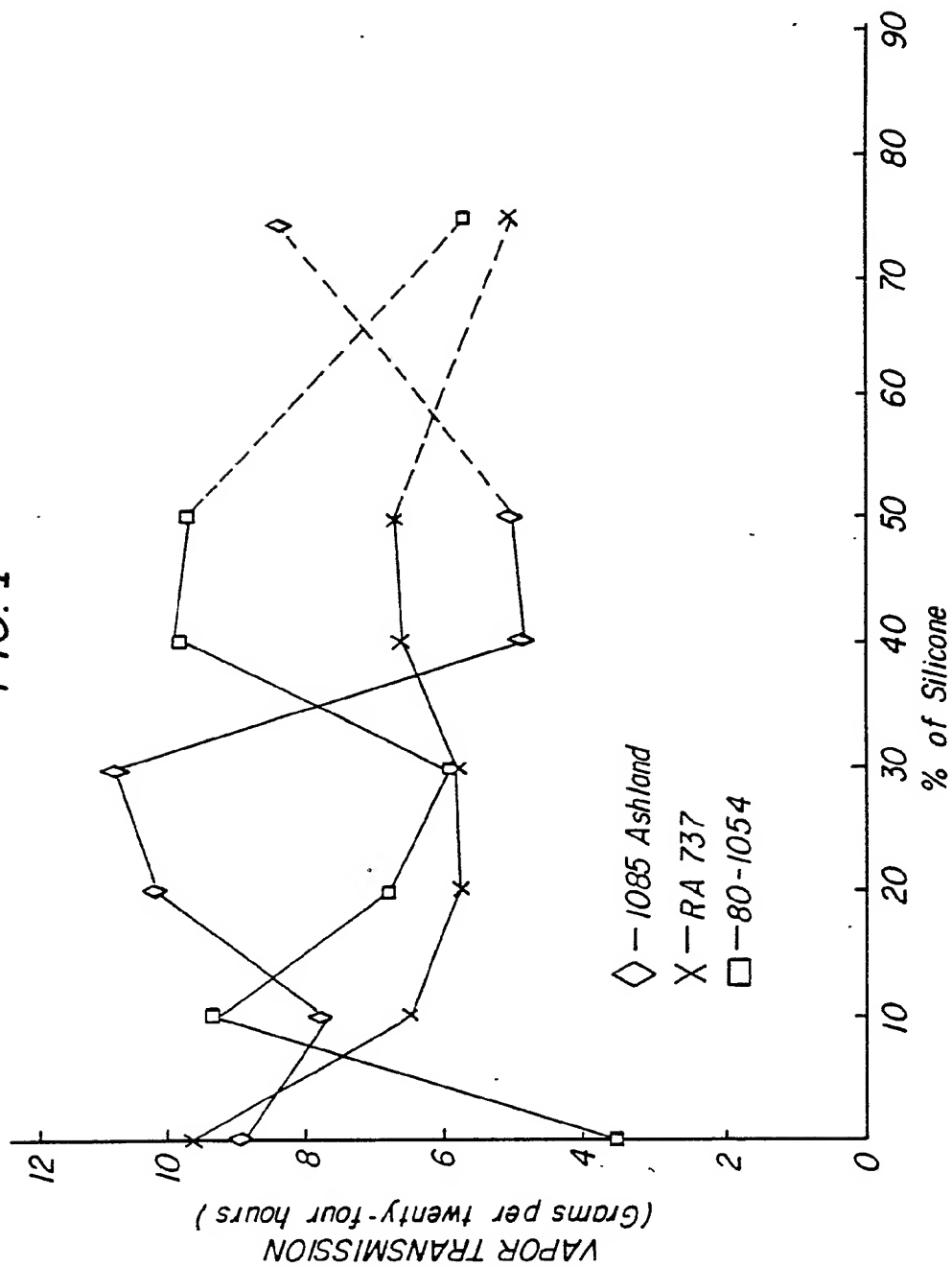
18. The method as defined in claim 16 wherein the vapor transmission through said adhesive increases and decreases in sawtooth fashion as the ratio of polysiloxane to said polymer increases.

19. The method of claim 16 wherein said cross-linked polysiloxane is up to 10 percent of said adhesive polymer.

20. The method of claim 16 wherein said cross-linked polysiloxane is up to 30 percent of the adhesive polymer.

1 / 2

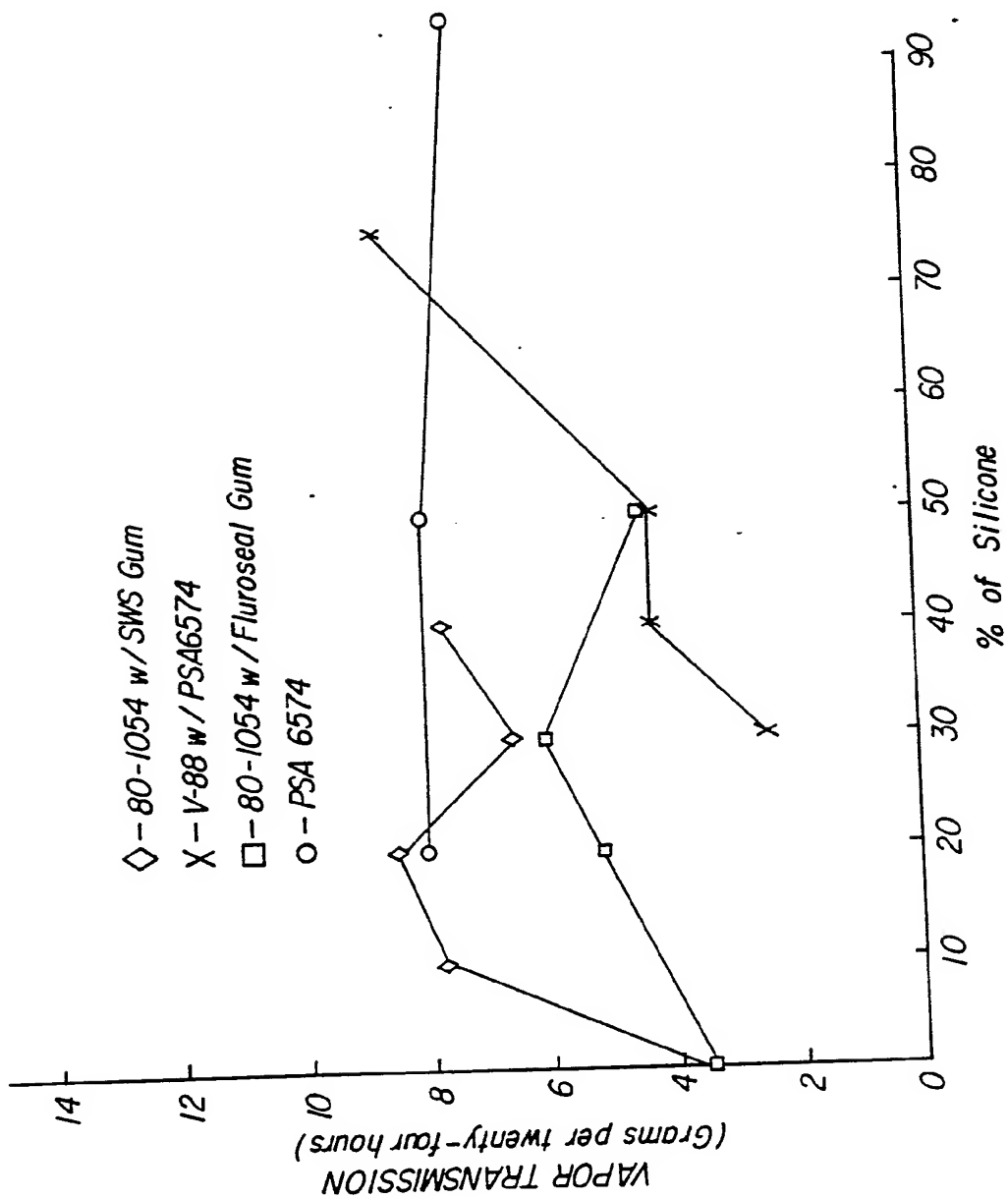
FIG. 1



SUBSTITUTE SHEET

2 / 2

FIG. 2



SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International Application No PCT/US85/02425

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³		
According to International Patent Classification (IPC) or to both National Classification and IPC		
INTL. CL. 4A61K 9/00		
US. 604/897		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System	Classification Symbols	
U.S.	604/890, 896, 897, 290-293, 303-307 128/Dig 21, 156 428/447 525/440, 453	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category *	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
X, Y	US, A, 3,929,704 30 December 1975 HORNING	1-15
Y	US, A, 3,679,458 25 July 1972 SORELL et al	2,10-14
Y	US, A, 4,370,358 25 January 1983 HAYES et al	3,5,6
X	US, A, 3,146,799 01 September 1964 FEKETE	1,11
Y	US, A, 2,857,356 21 October 1958 GOODWIN, Jr	1-6,9-12
Y	US, A, 4,460,371 17 July 1984 ABBEY	1-5,9-15
Y	US, A, 4,039,707 02 August 1977 O'MALLEY	1,11
Y	US, A, 2,736,721 28 February 1956 DEXTER	1,11
Y	US, A, 3,731,683 08 May 1973 ZAFFARONI	1,11,13-15
Y	US, A, 3,797,494 19 March 1974 ZAFFARONI	1,11,13-15
Y	US, A, 3,598,122 10 August 1971 ZAFFARONI	1,11,13-15
Y	US, A, 4,379,454 12 April 1983 CAMPBELL et al	1,11,13-15
Y	US, A, 4,201,211 06 May 1980 CHANDRASEKARAN et al	1,11,13-15
Y	US, A, 4,309,520 05 January 1982 BLIZZARD	1-3,11-13
A	US, A, 4,016,328 05 April 1977 HORNING	1-15
Y	US, A, 3,450,791 17 June 1969 SEKMAKAS et al	2,12
A	US, A, 3,983,298 28 September 1976 HAHN ET al	1,11
<p>* Special categories of cited documents: ¹⁵</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ²	Date of Mailing of this International Search Report ²	
12 February 1986	05 MAR 1986	
International Searching Authority ¹	Signature of Authorizing Officer ²⁰	
ISA/US	Jerome Robert Smith Jr.	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹⁰

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers because they relate to subject matter ¹² not required to be searched by this Authority, namely:

2. ☒ Claim numbers 16-20 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out ¹³, specifically:

These claims refer to a method in claim 10, however Claim 10 does not recite a method.

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ¹¹

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.